

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 85302708.4

(22) Date of filing: 17.04.85

(51) Int. Cl.⁴: **C 07 D 215/26**
C 07 C 93/08, A 61 K 31/135
A 61 K 31/47
//C07C97/00, C07C95/08

(30) Priority: 17.04.84 GB 8409908
 11.06.84 GB 8414858
 20.06.84 GB 8415761
 20.06.84 GB 8415762

(43) Date of publication of application:
 27.11.85 Bulletin 85/48

(84) Designated Contracting States:
 AT BE CH DE FR GB IT LI LU NL SE

(71) Applicant: **GLAXO GROUP LIMITED**
 Clarges House 6-12 Clarges Street
 London W1Y 8DH(GB)

(72) Inventor: **Skidmore, Ian Frederick**
 2 Wendover Drive
 Welwyn, Hertfordshire(GB)

(72) Inventor: **Naylor, Alan**
 35 Layston Park
 Royston, Hertfordshire(GB)

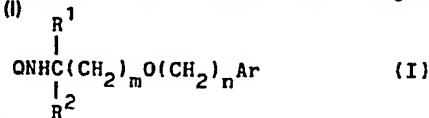
(72) Inventor: **Lunts, Lawrence Henry Charles**
 10 Wormley West End
 Broxbourne, Hertfordshire(GB)

(72) Inventor: **Finch, Harry**
 19 Hensley Close
 Hitchin, Hertfordshire(GB)

(74) Representative: **Marchant, James Ian et al,**
 Elkington and Fife High Holborn House 52/54 High
 Holborn
 London WC1V 6SH(GB)

(54) Ethanolamine compounds.

(57) The invention provides compounds of the general formula (I)



wherein

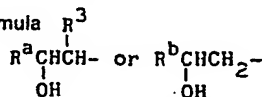
Ar represents a phenyl group optionally substituted by one or two substituents selected from halogen atoms, or C₁₋₃ alkyl or C₁₋₃ alkoxy groups, or by an alkylendioxy group of formula -O(CH₂)_pO- where p is 1 or 2;

R₁ and R₂ each represents a hydrogen atom or a C₁₋₃ alkyl group with the proviso that the sum total of carbon atoms in R₁ and R₂ is not more than 4;

m is an integer from 2 to 8 and

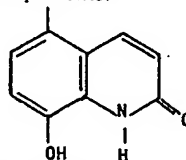
n is an integer from 1 to 7 with the proviso that the sum total of m + n is 4 to 12;

Q represents a group of formula

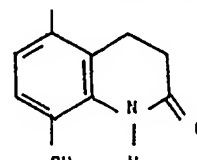


where

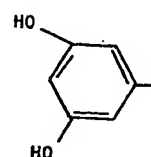
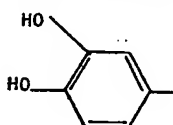
R^a represents a hydrogen atom or a C₁₋₃ alkyl group, R^b represents:



or



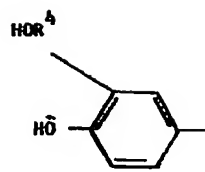
and R^b represents:



or

./...

EP 0 162 576 A1



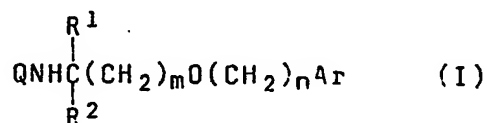
where R^1 represents a straight or branched C_{2-12} alkylene chain; and physiologically acceptable salts and solvates thereof.

The compounds of formula (I) have a selective stimulant action at β_2 -adrenoreceptors and are useful, in particular in the treatment of diseases associated with reversible airways obstruction such as asthma and chronic bronchitis.

ETHANOLAMINE COMPOUNDS

This invention relates to ethanolamine compounds having a stimulant action at β_2 -adrenoreceptors, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine.

Thus, the present invention provides compounds of the general formula (I)



wherein

Ar represents a phenyl group optionally substituted by one or two substituents selected from halogen atoms, or C_{1-3} alkyl or C_{1-3} alkoxy groups, or by an alkylenedioxy group of formula $-\text{O}(\text{CH}_2)_p\text{O}-$ where p is 1 or 2;

R^1 and R^2 each represents a hydrogen atom or a C_{1-3} alkyl group with the proviso that the sum total of carbon atoms in R^1 and R^2 is not more than 4;

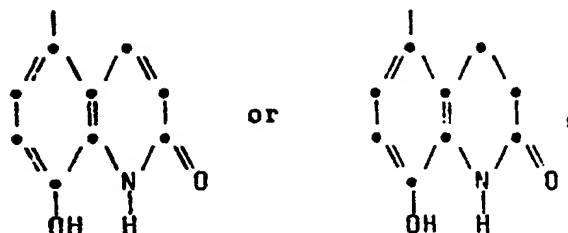
m is an integer from 2 to 8 and

n is an integer from 1 to 7 with the proviso that the sum total of m + n is 4 to 12;

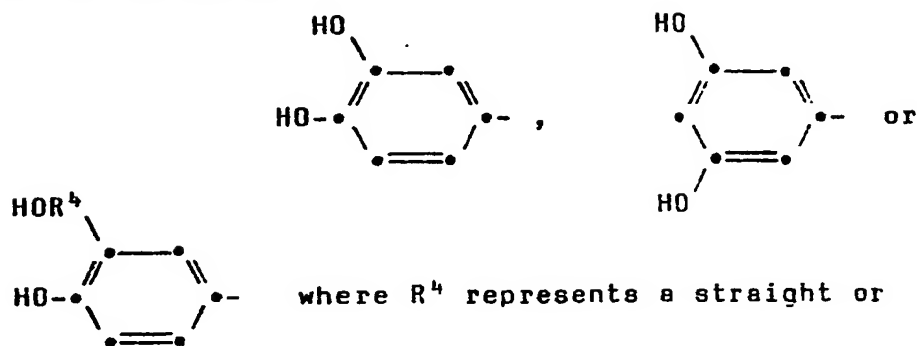
Q represents a group of formula $\begin{array}{c} \text{R}^3 \\ | \\ \text{R}^a\text{CHCH}- \\ | \quad | \\ \text{OH} \quad \text{OH} \end{array}$ or $\begin{array}{c} \text{R}^b\text{CHCH}_2- \\ | \\ \text{OH} \end{array}$,

where R^3 represents a hydrogen atom or a C_{1-3} alkyl group, R^a represents :

0162576



and R^b represents :



where R⁴ represents a straight or

branched C₂₋₃ alkylene chain;

and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

It will be appreciated that the compounds of general formula (I) possess one or more asymmetric carbon atoms, for example the carbon atom of the $\begin{array}{c} -CH- \\ | \\ OH \end{array}$ group and, when R¹

and R² are different groups or R³ is an alkyl group, the carbon atoms to which these are attached, and when R⁴ is a branched alkylene chain.

The compounds according to the invention thus include all enantiomers, diastereoisomers and mixtures thereof, including racemates. Compounds in which the carbon atom in the $\begin{array}{c} -CH- \\ | \\ OH \end{array}$ group is in the R configuration

are preferred.

In the general formula (I), the chain -(CH₂)_m- may be for example -(CH₂)₃-, -(CH₂)₄-, -(CH₂)₅-, -(CH₂)₆- or -(CH₂)₇-, and the chain -(CH₂)_n- may be for example -(CH₂)₂-, -(CH₂)₃-, -(CH₂)₄-, -(CH₂)₅- or -(CH₂)₆-. Preferably the total number of carbon atoms in the chains -(CH₂)_m- and -(CH₂)_n- is 6 to 12 inclusive and may be,

0162576

for example, 7, 8, 9 or 10. Compounds wherein the sum total of m and n is 7, 8 or 9 are particularly preferred.

R^1 and R^2 , for example, may each be methyl, ethyl, propyl or isopropyl groups except that if one of R^1 and R^2 is a propyl or isopropyl group, the other is a hydrogen atom or a methyl group. Thus for example R^1 may be a hydrogen atom or a methyl, ethyl or propyl group. R^2 , for example, may be a hydrogen atom or a methyl group. R^1 and R^2 are each preferably a hydrogen atom or a methyl group.

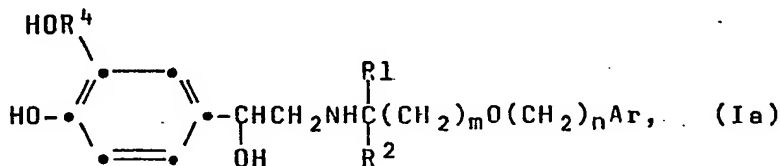
A preferred group of compounds is that wherein R^1 and R^2 are both hydrogen atoms, or R^1 is a hydrogen atom and R^2 is a C_{1-3} alkyl group, particularly a methyl group, or R^1 is a methyl group and R^2 is a methyl group.

Examples of the substituents which may be present on the phenyl group represented by Ar include chlorine, bromine, iodine, or in particular fluorine or chlorine atoms or methyl, ethyl, methoxy, or ethoxy groups.

Ar is preferably an unsubstituted phenyl group.

In the definition of Q in compounds of formula (I) the group R^3 may be for example a hydrogen atom or a methyl, ethyl, propyl or isopropyl group, particularly a hydrogen atom or a methyl or ethyl group. The chain R^4 may be for example $-(CH_2)_2-$, $-(CH_2)_3-$ or $-\underset{\text{CH}_3}{\text{CH}}-$.

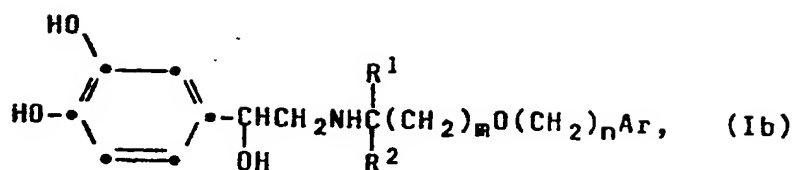
In one aspect, the invention provides a compound of formula (Ia):



[wherein R^1 , R^2 , R^4 , m, n and Ar are as defined for formula (I)].

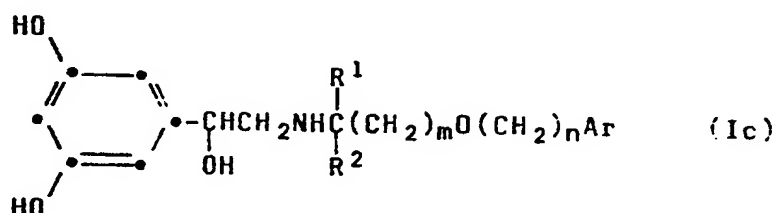
In another aspect, the invention provides a compound of formula (Ib)

0162576



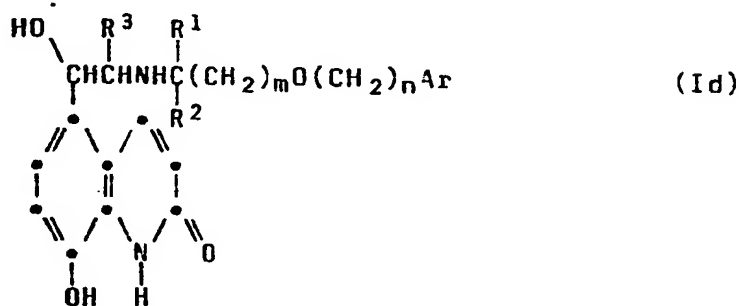
[wherein R^1 , R^2 , m , n and Ar are as defined for formula (I)].

In a further aspect, the invention provides a compound of formula (Ic)



[wherein R^1 , R^2 , m , n and Ar are as defined for formula (I)].

In yet another aspect, the invention provides a compound of formula (Id):



[wherein R^1 , R^2 , R^3 , R^4 , m , n and Ar are as defined for formula (I)].

Particularly important compounds of the invention include:-

2-Hydroxy-5-[1-hydroxy-2-[[6-[2-(4-methoxyphenyl)ethoxy]-hexyl]amino]ethyl]benzeneethanol;

2-Hydroxy-5-[1-hydroxy-2-[[1-methyl-6-(2-phenylethoxy)-hexyl]amino]ethyl]benzeneethanol;

0162576

5-[1-Hydroxy-2-[[1-methyl-6-(2-phenylethoxy)hexyl]amino]ethyl]-1,3-benzenediol;
5-[1-Hydroxy-2-[[6-(4-phenylbutoxy)hexyl]amino]ethyl]-1,3-benzenediol; and the physiologically acceptable salts and solvates thereof.

Suitable physiologically acceptable salts of the compounds of general formula (I) include acid addition salts derived from inorganic and organic acids, such as hydrochlorides, hydrobromides, sulphates, phosphates, maleates, tartrates, citrates, benzoates, 4-methoxybenzoates, 2- or 4-hydroxybenzoates, 4-chlorobenzoates, p-toluenesulphonates, methanesulphonates, ascorbates, salicylates, acetates, fumarates, succinates, lactates, glutarates, gluconates, tricarballates, hydroxy-naphthalenecarboxylates e.g. 1-hydroxy- or 3-hydroxy-2-naphthalenecarboxylates, or oleates. The compounds may also form salts with suitable bases. Examples of such salts are alkali metal (e.g. sodium and potassium), and alkaline earth metal (e.g. calcium or magnesium) salts.

The compounds according to the invention have a selective stimulant action at β_2 -adrenoreceptors, which furthermore is of a particularly advantageous profile. The stimulant action was demonstrated in the isolated trachea of the guinea-pig, where compounds were shown to cause relaxation of PGF₂ α -induced contractions. Compounds according to the invention have shown a particularly long duration of action in this test.

The selective action of compounds of the invention was demonstrated in the rat or guinea pig, where compounds were shown to have little or no effect on isolated rat or guinea pig atria (β_1 -adrenoreceptor tissues) at concentrations where they cause relaxation of PGF₂ α -contracted isolated trachea.

The compounds according to the invention may be used in the treatment of diseases associated with reversible airways obstruction such as asthma and chronic bronchitis.

0162576

The compounds according to the invention may also be used for the treatment of premature labour, depression and congestive heart failure, and are also indicated as useful for the treatment of inflammatory and allergic skin diseases, glaucoma, and in the treatment of conditions in which there is an advantage in lowering gastric acidity, particularly in gastric and peptic ulceration.

The invention accordingly further provides compounds of formula (I) and their physiologically acceptable salts and solvates for use in the therapy or prophylaxis of diseases associated with reversible airways obstruction in human or animal subjects. The invention also provides compounds of formula (I) and their physiologically acceptable salts and solvates and compositions containing them in association with instructions for their use in the therapy or prophylaxis of diseases associated with reversible airways obstruction in human or animal subjects.

The compounds according to the invention may be formulated for administration in any convenient way. The invention therefore includes within its scope pharmaceutical compositions comprising at least one compound of formula (I) or a physiologically acceptable salt or solvate thereof formulated for use in human or veterinary medicine. Such compositions may be presented for use with physiologically acceptable carriers or excipients, optionally with supplementary medicinal agents.

The compounds may be formulated in a form suitable for administration by inhalation or insufflation, or for oral, buccal, parenteral, topical (including nasal) or rectal administration. Administration by inhalation or insufflation is preferred.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs, with the use of a suitable propellant, such as dichlorodifluoromethane, trichlorofluoromethane, dichloro-

tetrafluoroethane, carbon dioxide or other suitable gas, or from a nebuliser. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount.

Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form in for example capsules or cartridges of e.g. gelatin, or blister packs from which the powder may be administered with the aid of an inhaler or insufflator.

For buccal administration the composition may take the form of tablets, drops or lozenges formulated in conventional manner.

The compounds of the invention may be formulated for parenteral administration. Formulations for injections may be presented in unit dosage form in ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

For topical administration the pharmaceutical composition may take the form of ointments, lotions or creams formulated in a conventional manner, with for example an aqueous or oily base, generally with the addition of suitable thickening agents and/or solvents. For nasal application, the composition may take the form of a spray, formulated for example as an aqueous solution or suspension or as an aerosol with the use of a suitable propellant.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention

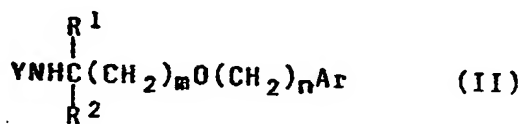
enemas, e.g. containing conventional suppository bases such as cocoa butter or other glyceride.

Where pharmaceutical compositions are described above for oral, buccal, rectal or topical administration, these may be presented in a conventional manner associated with controlled release forms.

A proposed daily dosage of active compound for the treatment of man is 0.0005mg to 100mg, which may be conveniently administered in one or two doses. The precise dose employed will of course depend on the age and condition of the patient and on the route of administration. Thus a suitable dose for administration by inhalation is 0.0005mg to 10mg, for oral administration is 0.02mg to 100mg, and for parenteral administration is 0.001mg to 2mg.

The compounds according to the invention may be prepared by a number of processes, as described in the following wherein Ar, Q, R^a, R^b, R¹, R², R³, R⁴, m and n are as defined for general formula (I) unless otherwise specified. In the general processes described below the final step in the reaction may be the removal of a protecting group.

According to one general process (1), a compound of general formula (I) may be obtained by reaction of an amine of general formula (II)



(wherein Y is a hydrogen atom or a group convertible thereto by catalytic hydrogenation) with a compound of formula $\text{R}^a\text{CH}=\text{CHR}^3$, $\text{R}^a\text{CH}(\text{OH})\text{CHR}^3\text{L}$, $\text{R}^b\text{CH}=\text{CH}_2$ or

$\text{R}^b\text{CH}(\text{OH})\text{CH}_2\text{L}$ (wherein L represents a leaving group, for

example a halogen atom such as chlorine, bromine or iodine, or a hydrocarbylsulphonyloxy group such as

methanesulphonyloxy or p-toluenesulphonyloxy followed by removal of any protecting groups where present, as described hereinafter.

The reaction may be effected in the presence of a suitable solvent for example an alcohol, such as ethanol, a halogenated hydrocarbon e.g. chloroform, a substituted amide e.g. dimethylformamide or an ether such as tetrahydrofuran or dioxan at a temperature from ambient to the reflux, optionally in the presence of a base such as an organic amine e.g. diisopropylethylamine or an inorganic base such as sodium carbonate.

Suitable Y groups convertible into a hydrogen atom include arylmethyl groups such as benzyl, benzhydryl, or α -methylbenzyl. Such groups may be removed by hydrogenolysis in the presence of a metal catalyst (e.g. palladium on charcoal).

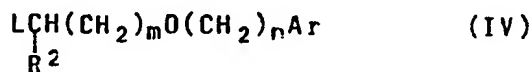
In another general process (2), a compound of general formula (I) may be prepared by alkylation. Conventional alkylation procedures may be used.

Thus, for example, in one process (a), a compound of general formula (I) in which R^1 is a hydrogen atom may be prepared by alkylation of an amine of general formula (III)



(wherein R^5 is a hydrogen atom or a protecting group and R^6 is a hydrogen atom) followed by removal of any protecting group where present.

The alkylation (a) may be effected using an alkylating agent of general formula (IV):



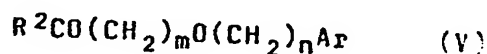
(wherein L is as previously defined).

The alkylation is preferably effected in the presence of a suitable acid scavenger, for example, inorganic bases such as sodium or potassium carbonate, organic bases such as triethylamine, diisopropylethylamine or pyridine, or

0162576

alkylene oxides such as ethylene oxide or propylene oxide. The reaction is conveniently effected in a solvent such as acetonitrile or an ether e.g. tetrahydrofuran or dioxan, a ketone e.g. butanone or methyl isobutyl ketone, a substituted amide e.g. dimethylformamide or a chlorinated hydrocarbon e.g. chloroform at a temperature between ambient and the reflux temperature of the solvent.

According to another example (b) of an alkylation process, a compound of general formula (I) in which R¹ represents a hydrogen atom may be prepared by alkylation of an amine of general formula (III), as previously defined except that R⁶ is a hydrogen atom or a group convertible thereto under the reaction conditions, with a compound of general formula (V):



in the presence of a reducing agent, followed when necessary by removal of any protecting groups.

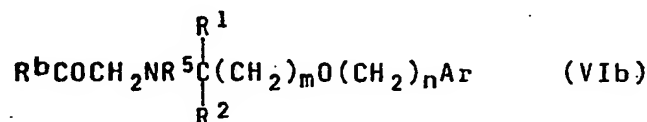
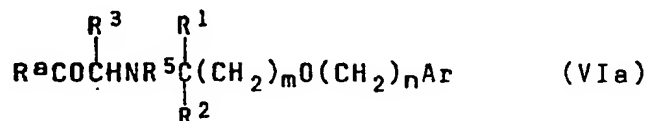
Suitable reducing agents include hydrogen in the presence of a metal catalyst such as platinum, platinum oxide, palladium, Raney nickel or rhodium, on a support such as charcoal, using an alcohol, e.g. ethanol or an ester e.g. ethyl acetate or an ether e.g. tetrahydrofuran, or water, as reaction solvent, or a mixture of solvents, e.g. a mixture of two or more of those just described at normal or elevated temperature and pressure, for example from 20 to 100°C and from 1 to 10 atmospheres.

Alternatively when one or both of R⁵ and R⁶ are hydrogen atoms, the reducing agent may be a hydride such as diborane or a metal hydride such as sodium borohydride, sodium cyanoborohydride or lithium aluminium hydride.

Suitable solvents for the reaction with these reducing agents will depend on the particular hydride used, but will include alcohols such as methanol or ethanol, or ethers such as diethyl ether or tert-butyl methyl ether, or tetrahydrofuran.

Where it is desired to use a protected intermediate of general formula (III) it is particularly convenient to use hydrogen and a metal catalyst as described above with protecting groups R^5 and R^6 which are capable of being converted to a hydrogen atom under these reducing conditions. Suitable protecting groups of this type include arylmethyl groups such as benzyl, benzhydryl and α -methylbenzyl.

In a third general process (3), a compound of general formula (I) may be prepared by reduction. Thus, in one example a compound of general formula (I) may be prepared by reducing an intermediate ketone of formulae (VIa) or (VIb):

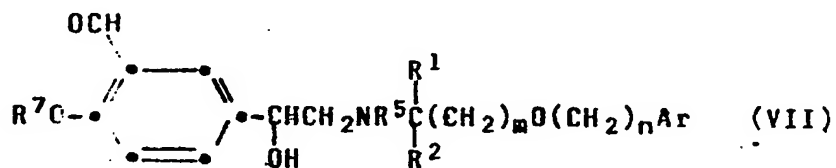


[wherein R^5 is as defined for general formula (III)] followed where necessary by removal of any protecting groups.

The reduction may be effected using reducing agents conventionally employed for the reduction of ketones, for example hydrogen in the presence of a metal catalyst. Alternatively the reducing agent may be for example a hydride such as diborane or a metal hydride such as lithium aluminium hydride, sodium bis(2-methoxyethoxy)-aluminium hydride, sodium borohydride or aluminium hydride. The reaction may be effected in a solvent, where appropriate an alcohol e.g. methanol or ethanol, or an ether such as tetrahydrofuran, or a halogenated hydrocarbon such as dichloromethane.

0162576

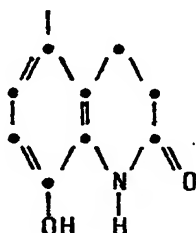
In another process, a compound of general formula (I) wherein R^4 is $-\text{CH}(\text{CH}_3)-$ may be prepared by reaction of an aldehyde of general formula (VII):



(wherein R^5 is as previously defined and R^7 is a hydrogen atom or a protecting group) with a Grignard reagent such as methyl magnesium chloride in a solvent such as tetrahydrofuran, followed when necessary by removal of any protecting groups. Suitable protecting groups R^7 are tetrahydropyranyl or aralkyl groups such as benzyl, α -methylbenzyl, diphenylmethyl or triphenylmethyl. When R^7 is a tetrahydropyranyl group this may be cleaved by hydrolysis under acidic conditions. When R^7 is an aralkyl group this may be cleaved by hydrogenolysis as previously described for the groups R^5 and R^6 .

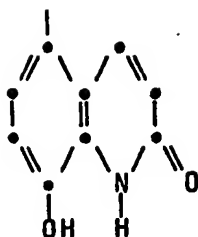
It is also possible to prepare a compound of general formula (I) by a process comprising interconversion of another compound of general formula (I).

In one example, a compound of formula (I) in which R^8 is the group :



may be prepared by reduction of a corresponding compound in which R^8 is the group :

0162576



using for example hydrogen in the presence of a metal catalyst.

In the general processes described above, the compound of formula (I) obtained may be in the form of a salt, conveniently in the form of a physiologically acceptable salt. Where desired, such salts may be converted to the corresponding free bases using conventional methods.

Physiologically acceptable salts of the compounds of general formula (I) may be prepared by reacting a compound of general formula (I) with an appropriate acid or base in the presence of a suitable solvent such as acetonitrile, acetone, chloroform, ethyl acetate or an alcohol, e.g. methanol, ethanol or iso-propanol.

Physiologically acceptable salts may also be prepared from other salts, including other physiologically acceptable salts, of the compounds of general formula (I), using conventional methods.

When a specific enantiomer of a compound of general formula (I) is required, this may be obtained by resolution of a corresponding racemate of a compound of general formula (I) using conventional methods.

Thus, in one example an appropriate optically active acid may be used to form salts with the racemate of a compound of general formula (I). The resulting mixture of isomeric salts may be separated for example by fractional crystallisation, into the diastereoisomeric salts from which the required enantiomer of a compound of general formula (I) may be isolated by conversion into the required free base.

Alternatively, enantiomers of a compound of general formula (I) may be synthesised from the appropriate optically active intermediates using any of the general processes described herein.

Specific diastereoisomers of a compound of formula (I) may be obtained by conventional methods, for example by synthesis from an appropriate asymmetric starting material using any of the processes described herein, or by conversion of a mixture of isomers of a compound of general formula (I) into appropriate diastereoisomeric derivatives e.g. salts which then can be separated by conventional means e.g. by fractional crystallisation. Alternatively, in some instances a specific diastereoisomer may be obtained through the use of particular process conditions, for example the diastereoisomers obtained from ketones of formula (VIa) where R^3 is an alkyl group may be determined by the method of reduction chosen. Racemates of diastereoisomers may be obtained by conventional methods of separation e.g. fractional crystallisation of a mixture of isomers of compounds of formula (I) or the salts thereof.

The intermediate compounds of formula $R^aCHCH(R^3)L$ and R^bCHCH_2L and OH

R^bCHCH_2L may be prepared from the corresponding OH haloketones $R^aCOCH(R^3)Hal$ and R^bCOCH_2Hal by reduction using for example a metal hydride such as sodium borohydride in a solvent such as ethanol. The halogen atom may be displaced to yield intermediates where L is a leaving group other than a halogen atom.

Compounds of formula $R^aCH-CH(R^3)$ and R^bCHCH_2

may be prepared from the corresponding compounds $R^aCHCH(R^3)L$ and R^bCHCH_2L and OH OH

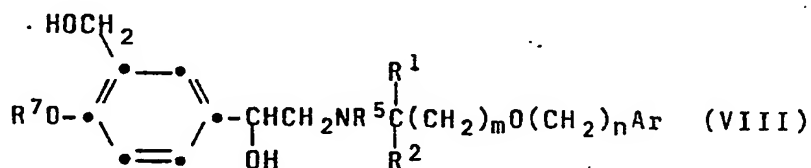
by treatment with base, for example an amine, which may be for example a compound of general formula (II), or an

inorganic base such as sodium hydroxide in a solvent such as ethanol.

Intermediates of formula (III) and intermediate ketones of formulae R^aCOCHR^3Hal and R^bCOCH_2Hal are either known compounds or may be prepared by analogous methods to those used for the preparation of the known compounds.

Intermediate ketones of formulae (VIa) and (VIb) may be prepared from ketones of formulae R^aCOCHR^3Hal and R^bCOCH_2Hal by reaction with an amine of formula (II). The reaction may be effected in a cold or hot solvent, for example tetrahydrofuran, tert-butyl methyl ether, dioxan, chloroform, dimethylformamide, acetonitrile or a ketone such as butanone or methylisobutylketone, or an ester, for example ethyl acetate optionally in the presence of a base such as diisopropylethylamine, sodium carbonate or other acid scavenger such as propylene oxide.

Intermediate aldehydes of formula (VII) may be prepared by oxidation of an alcohol of formula (VIII):



using an oxidising agent such as activated manganese dioxide in a solvent such as dichloromethane.

Intermediates of formulae (II), (IV), (V) and (VIII) may be prepared by the general methods described in U.K. Patent Specification No. 2140800A.

0162576

The following examples illustrate the invention. Temperatures are in °C. Thin layer chromatography (T.l.c.) was carried out over SiO₂. "Dried" refers to drying using magnesium sulphate except where otherwise stated.

The following abbreviations are used: EA - ethyl acetate; ER - diethyl ether, DMF - dimethylformamide; THF - tetrahydrofuran; [FC] - flash column chromatography on silica (Merck 9385); [C] - column chromatography on silica (Merck 9385). The preparation of the following intermediates is described in U.K. Patent Specification 2140800A.

Intermediate 1

7-[2-(Phenylethoxy)]-2-heptanone

Intermediate 2

N-[6-(3-Phenylpropoxy)hexyl]benzenemethanamine hydrobromide

Intermediate 7

4-Hydroxy- α^1 -[(phenylmethyl)-6-[3-(phenylpropoxy)hexyl]amino]methanol-1,3-benzenedimethanol

Intermediate 10

[4-[(5-Bromopentyl)oxy]butyl]benzene

Intermediate 11

1-[2-[(6-Bromohexyl)oxy]ethyl]-4-methoxybenzene

Intermediate 17

N-[6-(4-Phenylbutoxy)hexyl]benzenemethanamine

Intermediate 21

[4-[(6-Bromohexyl)oxy]butyl]benzene

Intermediate 23

[2-[(6-Bromohexyl)oxy]ethyl]benzene

Intermediate 311,1-Dimethyl-6-(2-phenylethoxy)hexamineIntermediate 31-[3-[2-(Acetyloxy)ethyl]-4-hydroxyphenyl]-2-bromoethanone

A solution of bromine (0.8ml, 2.5g) in chloroform (20ml) was added over 20min to a stirred solution of 1-[3-[2-(acetyloxy)ethyl]-4-hydroxyphenyl]ethanone (3.26g) in chloroform (50ml) containing a few drops of 45% hydrogen bromide in acetic acid. The red solution was diluted with ER (200ml) washed with water (100ml), 8% sodium bicarbonate (100ml), brine (100ml), dried and evaporated to give the title compound as an oil which solidified on standing to give a pale pink solid (4.1g) m.p. 89-92°. Two recrystallisations from chloroform gave a sample with m.p. 98-99°.

Intermediate 42-Bromo-1-[4-hydroxy-3-(2-hydroxyethyl)phenyl]ethanone

A solution of Intermediate 3 (3.5g) in methanol (40ml) was diluted with 2M hydrochloric acid (10ml) and the mixture was refluxed for 1h. The mixture was evaporated in vacuo, to remove most of the methanol, and the residue was diluted with water (50ml) and extracted with ER (2x50ml). The extract was washed with 8% sodium bicarbonate (50ml), brine (50ml), dried and evaporated to give the title compound as an oil which solidified on standing to give a buff solid (2.05g) m.p. 124-125°. Recrystallisation from chloroform gave a sample with m.p. 130-131°.

Intermediate 51-[4-Hydroxy-3-(2-hydroxyethyl)phenyl]-2-[(phenylmethyl)[6-(3-phenyl-propoxy)hexyl]amino]ethanone

A mixture of Intermediate 4 (1.0g), Intermediate 2 (1.25g) and N,N-diisopropylethylamine (0.8g) in chloroform (10ml) was stirred at 23° for 18h. The mixture was diluted with ER (60ml) and washed with water (2x25ml), brine (20ml), dried and evaporated to give an oil. Purification by [FCS] eluting with ER afforded the title compound as a viscous yellow oil (0.95g). T.l.c. (ER) Rf 0.63.

0162576

Intermediate 6N-[1-Methyl-6-(2-phenylethoxy)hexyl]benzenemethanamine

A solution of Intermediate 1 (11.7g) and benzylamine (5.35g) in toluene (50ml) was stirred and heated under nitrogen for 2h. The solution was hydrogenated at atmospheric pressure and room temperature over a pre-reduced 5% platinum oxide on carbon catalyst (1.5g) in ethanol (50ml) until the uptake of hydrogen ceased. The catalyst was removed by filtration through Hyflo and the solvent evaporated in vacuo at 50°. The crude product was purified by [FCS] elution with 5% ethanol/toluene affording the title compound as a colourless oil (10.8g). For analytical purposes, a portion was converted to the fumarate salt by treating the amine (325mg) with a solution of fumaric acid (116mg) in a mixture of ER (10ml) and methanol (2ml). The solution was evaporated in vacuo at 40° to yield a viscous oil which when triturated with ER (10ml) afforded the fumarate salt of the title compound as a white powder. Recrystallisation from EA gave a colourless crystalline powder (335mg) m.p. 91-94°.

Intermediate 82-Hydroxy-5-[1-hydroxy-2-[(phenylmethyl)[6-(3-phenylpropoxy)hexyl]amino]ethyl]benzaldehyde

Activated manganese dioxide (ca 10g) was added in 2g portions to a stirred solution of Intermediate 7 (2.5g) in dichloromethane (100ml). Five minutes after each addition the reaction was monitored by t.l.c. (ER) and no more manganese dioxide was added when most of the starting material (Rf 0.63) had been converted into the product (Rf 0.39). The mixture was filtered through hyflo and the filtrate was evaporated to give an oil which was purified by [FCS] eluting with ER-cyclohexane (1:1) to give the title compound as a yellow oil (1.5g).

T.l.c. (ER-cyclohexane 1:1) Rf 0.63.

Intermediate 94-Hydroxy- α^3 -methyl- α^1 -[[[(phenylmethyl)[6-(3-phenylpropoxy)hexyl]-amino]methyl]-1,3-benzenedimethanol

A solution of methyl magnesium chloride in THF (2.9M, 5ml) was added dropwise to a stirred solution of Intermediate 8 (1.1g) in dry THF (20ml) at 23° under nitrogen. The mixture was stirred at 23° for 0.5h, diluted with saturated aqueous ammonium chloride (80ml) and extracted with EA (2x50ml). The organic phase was washed with brine

0162576

(25ml), dried and evaporated to give the title compound as a yellow oil (1.1g). T.l.c. (ER) Rf 0.71.

Intermediate 12

N-[5-(4-(Phenylbutoxy)pentyl)benzenemethanamine

Intermediate 10 (4.0g) was added dropwise to benzylamine (20ml) at 110°. The solution was heated at 110-120° for 90min, cooled, hydrochloric acid (2M; 125ml) was added and the mixture was extracted with EA (2x100ml). The organic extract was washed with aqueous sodium carbonate (100ml) and brine (100ml), dried and evaporated. The residue was distilled to give the title compound as a colourless oil (3.3g), b.p. 190-195°/0.1mmHg. T.l.c. (cyclohexane-ER 1:1) Rf 0.25

Intermediate 13

N-[6-[2-(4-Methoxyphenyl)ethoxy]hexyl]benzenemethanamine hydrochloride

Intermediate 11 (6g) and benzylamine (10.2g) were stirred together at 120° for 3h. The mixture was cooled, diluted with ER (200ml) and washed with 2N hydrochloric acid (200ml). Both phases were filtered to afford the crude product which was dried in vacuo at 40° and recrystallised from EA-hexane to give the title compound as a white solid (5.52g), m.p. 109-110°.

Intermediate 14

1-[4-Hydroxy-3-(2-hydroxyethyl)phenyl]-2-[(phenylmethyl)[5-(4-phenylbutoxy)pentyl]amino]ethanone

Intermediate 4 (1g), Intermediate 12 (1.26g) and N,N-diisopropylethylamine (1g) in THF (15ml) were stirred at reflux under nitrogen for 5h, and left at room temperature overnight. The mixture was diluted with dichloromethane (30ml), washed with 2N hydrochloric acid (10ml), dried (Na₂SO₄) and evaporated in vacuo to give an oil. Purification by [FCS] (triethylamine deactivated silica) eluting with toluene-ethanol (20:1) gave a yellow oil (1.49g).

T.l.c. triethylamine deactivated silica (Toluene-ethanol 100:5) Rf 0.18

Intermediate 15

1-[4-Hydroxy-3-(2-hydroxyethyl)phenyl]-2-[6-[(4-methoxyphenyl)ethoxy]

hexyl](phenylmethyl)amino]ethanone (1.09g) T.l.c. (toluene-ethanol-0.88 ammonia soln 39:10:1) Rf 0.45 was prepared in a similar manner to Intermediate 14 from Intermediate 4 (1g) and Intermediate 13 (1.32g).

Intermediate 16

1-[4-Hydroxy-3-(2-hydroxyethyl)phenyl]-2-[[1-methyl-6-(2-phenylethoxy)hexyl](phenylmethyl)amino]ethanone, (0.61g) was prepared in a similar manner to Intermediate 14 from Intermediate 4 (1.2g) and Intermediate 6 (1.26g).

T.l.c. (Toluene:ethanol:0.88 NH₃ 39:10:1) Rf 0.42.

Intermediate 18

1-(3,4-Dihydroxyphenyl)-2-[[6-(4-phenylbutoxy)hexyl](phenylmethyl)amino]ethanone

A solution of α -chloro-3,4-dihydroxyacetophenone (1.5g), Intermediate 17 (3.6g) and N,N-diisopropylethylamine (1.8g) in THF (10ml) was kept at 23° for 4 days. ER (70ml) was added and the mixture was washed with 8% sodium bicarbonate (4x50ml), brine (50ml), dried and evaporated to give an oil. Purification by [FCS] using cyclohexane-ER (2:3) as eluant gave the title compound as a yellow oil (1.2g).

T.l.c. (ER-cyclohexane 3:2) Rf 0.28.

Intermediate 19

N-[5-(4-(Phenylbutoxy)pentyl]benzenemethanamine

Intermediate 10 (4.0g) was added dropwise to benzylamine (20ml) at 110°. The solution was heated at 110-120° for 90min and cooled. Hydrochloric acid (2M; 125ml) was added and the mixture was extracted with EA (2x100ml). The organic extract was washed with aqueous sodium carbonate (100ml) and brine (100ml), dried and evaporated. The residue was distilled to give the title compound as a colourless oil (3.3g) b.p. 190-195°/0.1mmHg.

T.l.c. (Cyclohexane-ER 1:1) Rf 0.25

Intermediate 20

1-[3,4-Dihydroxyphenyl]-2-[[5-(4-phenylbutoxy)pentyl](phenylmethyl)amino]ethanone

A solution of 2-chloro-3',4'-dihydroacetophenone (1.29g), Intermediate 19 (2.26g) and N,N-diisopropylethylamine (2.69g) in dichloromethane

(20ml) was stirred under nitrogen for 20h. Potassium iodide (1.15g) was added, the mixture stirred for a further 6h, diluted with dichloromethane (200ml) and washed successively with 2N hydrochloric acid (100ml), 8% sodium bicarbonate (100ml) then dried (Na_2SO_4). Concentration in vacuo gave the crude product which was purified by [FCS] (triethylamine deactivated silica) eluting with toluene-ethanol (19:1) to give the title compound as a brown oil (1.95g).

Intermediate 22

α -[[[6-(4-Phenylbutoxy)hexyl]amino]methyl]-3,5-bis(phenylmethoxy)benzenemethanol.

α -(Aminomethyl)-3,5-bis(phenylmethoxy)benzenemethanol (1.56g), Intermediate 21 (1.16g) and N,N-diisopropylethylamine (0.94ml) in DMT (15ml) were stirred at 100° under nitrogen (80ml) for 2h. Saturated aqueous sodium bicarbonate was added and the mixture extracted with EA (3x100ml). The combined extracts were washed with water (80ml), dried and evaporated to give a yellow oil. The crude oil in EA was purified by [FCS] eluting with EA - triethylamine (99:1) to give the title compound as a white solid (0.7g), m.p. $65-67^\circ$.

Intermediate 24

N-[6-(2-Phenylethoxy)hexyl]benzenemethanamine

Intermediate 23 (4.0g) was added dropwise to benzylamine (20ml) at 110° . The solution was heated at $110-120^\circ$ for 90min, cooled, and treated with hydrochloric acid (2M; 125ml). The mixture was extracted with EA (2x100ml) and the extract was washed with aqueous sodium carbonate (100ml) and brine (100ml), dried and evaporated. Distillation of the residue gave the title compound as a colourless oil (3.2g) b.p. $180-190^\circ/0.1\text{mmHg}$ T.l.c. (Cyclohexane - ER 1:1) Rf 0.2

Intermediate 25

α -[[[6-(2-Phenylethoxy)hexyl](phenylmethyl)amino]methyl]-3,5-bis(phenylmethoxy)benzenemethanol

A solution of 2-[3,5-bis(phenylmethoxy)phenyl]oxirane (1.0g) and Intermediate 24 (1.0g) in methanol (20ml) was refluxed for 18h and evaporated. The residue was purified by [C] eluting with cyclohexane-

ER (3:1). Repeated [C] eluting with chloroform gave the title compound as a colourless oil (0.8g). T.l.c. (Cyclohexane - ER 3:1) Rf 0.2

Intermediate 26

2-[[5-(4-Phenylbutoxy)pentyl](phenylmethyl)amino]-1-[3,5-bis(phenylmethoxy)phenyl]ethanone

A solution of 2-bromo-1-[3,5-bis(phenylmethoxy)phenyl]ethanone (2.45g) Intermediate 19 (2.0g) and N,N-diisopropylethylamine (0.774g) in dichloromethane (20ml) was stirred for 20h at room temperature. ER (150ml) was added and the mixture was washed with water, dried (Na_2SO_4), and evaporated. The residue was purified by [C] eluting with cyclohexane - ER (9:1) to give the title compound as a yellow oil (2.4g).

T.l.c. (Cyclohexane - ER 3:1) Rf 0.4.

Intermediate 27

1-[2-(4-Bromobutoxy)ethyl]-4-fluorobenzene

A mixture of 4-fluorobenzeneethanol (10.0g), 1,4-dibromobutane (59.0g), aqueous sodium hydroxide (50% w/v; 40ml) and tetrabutylammonium bisulphate (1g) was stirred at room temperature for 20h, diluted with water (50ml) and extracted with ER (2x100ml). The dried extract was evaporated and the residue was purified by [C] eluting with cyclohexane followed by cyclohexane-ER (19:1) to give the title compound as a colourless oil (17.3g).

T.l.c. (cyclohexane - ER 9:1) Rf 0.4

Intermediate 28

7-[2-(4-Fluorophenyl)ethoxy]-2-heptanone

A mixture of Intermediate 27 (10.0g), acetylacetone (5.0g), potassium iodide (8.3g), potassium carbonate (5.52g) and ethanol (75ml) was refluxed for 22h, filtered, and evaporated. The residue was treated with ER (200ml), filtered and evaporated. The resulting oil was purified by [C] eluting with cyclohexane - ER (4:1) to give the title compound as a colourless oil (4.3g).

T.l.c. (cyclohexane - ER 3:1) Rf 0.25.

Intermediate 291-[[2-(4-Bromobutoxy)]ethyl]-4-methoxybenzene

4-Methoxybenzeneethanol (20g), 1,4-dibromobutane (99.31g), tetrabutylammonium bisulphate (5.92g) and 50% sodium hydroxide solution (200ml) were stirred at room temperature for 18h. The mixture was diluted with water (300ml) and extracted with ER (2x400ml), dried and evaporated in vacuo to give a colourless oil (39.4g). Purification by [FCS] eluting with cyclohexane - ER (100:0 → 90:10) gave the title compound as a colourless oil (30.9g). T.l.c. (cyclohexane - ER 9:1) Rf 0.36.

Intermediate 307-[2-(4-Methoxyphenyl)ethoxy]-2-heptanone

A mixture of Intermediate 29 (12.0g), acetylacetone (6.0g), potassium iodide (13.3g), potassium carbonate (6.95g), and ethanol (75ml) was refluxed for 18h, filtered, and evaporated. The residue was treated with ER (200ml), filtered, and evaporated. The resulting oil was purified by [C] eluting with cyclohexane - ER (4:1) to give the title compound as a colourless oil (4.7g).

T.l.c. (cyclohexane - ER 3:1) Rf 0.25.

Intermediate 32N-[1,1-Dimethyl-6-(2-phenylethoxy)hexyl]benzenemethanamine

A solution of Intermediate 31 (2.3g), benzaldehyde (1.27g) and 4-toluenesulphonic acid (0.02g) in toluene (150ml) was refluxed for 18h and evaporated. The residue in ethanol (50ml) was hydrogenated over 5% platinum on charcoal (0.4g) for 2h, filtered and evaporated. The resulting oil was purified by [C] eluting with cyclohexane-ER (3:1) to give the title compound as a colourless oil (2.1g).

T.l.c. (cyclohexane-ER 3:1) Rf 0.2

Intermediate 332-[[1,1-Dimethyl-6-(2-phenylethoxy)hexyl](phenylmethyl)amino-1-[3,5-bis(phenylmethoxy)phenyl]ethanone

A solution of 2-bromo-1-[3,5-bis(phenylmethoxy)phenyl]ethanone (2.5g), Intermediate 32 (2.0g) and N,N-diisopropylethylamine (0.77g) in THF (25ml) was stirred at room temperature for 2h and refluxed for 20h.

ER (100ml) was added and the resulting suspension was filtered, the filtrate was evaporated and the residue was purified by [C] eluting with cyclohexane-ER (4:1) to give the title compound as a pale yellow oil (1.2g). T.l.c. (cyclohexane-ER 3:1) Rf 0.4

Intermediate 34

α -[[[6-[2-(4-methoxyphenyl)ethoxy]hexyl](phenylmethyl)amino]methyl]-3,4-bis(phenylmethoxy)benzenemethanol

A solution of 1 bromo-2-[3,4-bis(phenylmethoxy)phenyl]ethanone (1.0g), Intermediate 13, free base (0.83g) and N,N-diisopropylethylamine (0.55g) in THF (15ml) was stirred under nitrogen for 18h. The solvent was evaporated in vacuo to give an oil which was dissolved in EA (50ml) and washed with 2N hydrochloric acid (50ml). The aqueous phase was re-extracted with EA (20ml), the organic phases combined, dried (Na_2SO_4) and evaporated in vacuo to give a yellow oil which was purified by [FCS] (triethylamine deactivated silica) eluting with cyclohexane-EA (1:1). The resulting yellow oil was dissolved in absolute ethanol (25ml) and THF (5ml), the solution treated at 0° under nitrogen with sodium borohydride (0.115g). The mixture was stirred under nitrogen for 44h, diluted with 2N hydrochloric acid (5ml) and the solvent evaporated in vacuo at 40° . The residue was partitioned between 2N sodium bicarbonate solution (10ml) and EA (50ml), the aqueous layer extracted with further EA (20ml) and the combined organic extracts dried (Na_2SO_4) and evaporated in vacuo to give a yellow oil which was purified by [FCS] eluting with cyclohexane-EA (3:1) to give the title compound as a yellow oil (0.96g).

T.l.c. (cyclohexane-EA 3:1) Rf 0.24.

Example 1

2-Hydroxy-5-[1-hydroxy-2-[[6-(3-phenylpropoxy)hexyl]amino]ethyl]-benzeneethanol

A solution of Intermediate 5 (0.5g) in absolute ethanol (25ml) was hydrogenated at room temperature and atmospheric pressure over 10% palladium on carbon and 10% platinum on carbon catalysts (0.15g of each). When hydrogen absorption (49ml) ceased the mixture was filtered and the filtrate evaporated to give an oil. Purification by [FCS] (triethylamine-deactivated silica) eluting with EA (9:1)

afforded the title compound as an oil which on trituration with ER gave a white solid (0.31g) m.p. 64-65⁰.

T.l.c. triethylamine-deactivated silica (EA-methanol 9:1) Rf 0.21

Example 2

4-Hydroxy- α^3 -methyl- α^1 -[[6-(3-phenylpropoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, (0.52g) was prepared in a similar manner to Example 1 from Intermediate 9 (1.1g).

T.l.c. triethylamine-deactivated silica (EA-methanol 9:1) Rf 0.4.

Example 3

2-Hydroxy-5-[1-hydroxy-2-[[5-(4-phenylbutoxy)pentyl]amino]ethyl]benzeneethanol

A solution of Intermediate 14 (1.36g) in absolute ethanol (55ml) was hydrogenated over a mixture of 10% palladium on charcoal (140mg) and 5% platinum on charcoal (140mg) catalysts. The mixture was filtered through hyflo and evaporated in vacuo to give a colourless oil (1.12g). Trituration with ER afforded the title compound as a white solid (0.6g) m.p. 65-67⁰.

Analysis Found: C, 71.95; H, 8.68; N, 3.45.

C₂₅H₃₇NO₄ requires C, 72.25; H, 8.97; N, 3.37%.

Example 4

2-Hydroxy-5-[1-hydroxy-2-[[6-[2-(4-methoxyphenyl)ethoxy]hexyl]amino]ethyl]benzeneethanol (0.42g) was prepared in a similar manner to

Example 3 from Intermediate 15 (0.79g). m.p. 84-85⁰.

T.l.c. (toluene-ethanol-0.88 ammonia solution 39:10:1) Rf 0.28.

Example 5

2-Hydroxy-5-[1-hydroxy-2-[[1-methyl-6-(2-phenylethoxy)hexyl]amino]ethyl]benzeneethanol hydrochloride (4:3)

A solution of Intermediate 16 (1g) in absolute ethanol (40ml) was hydrogenated over a mixture of pre-reduced 10% palladium on charcoal (100mg) and 5% platinum on charcoal (100mg) catalysts in absolute ethanol (10ml) until the uptake of hydrogen (78ml) ceased. The mixture was filtered through Hyflo and evaporated in vacuo to give a yellow oil (0.81g). Purification by [FCS] (triethylamine deactivated

silica) eluting with toluene-ethanol (19:1) gave a yellow oil (0.81g) which was triturated with ethereal hydrogen chloride to give the title compound as an off-white solid (0.29g) m.p. 97-100°.

T.l.c. silica (Toluene:ethanol:0.88 NH₃ 39:10:1) Rf 0.33

Example 6

8-Hydroxy-5-[1-hydroxy-2-[[1-methyl-6-(2-phenylethoxy)hexyl]amino]ethyl]-2(1H)-quinolinone

A slurry of 8-hydroxy-5-[[1-(phenylmethyl)amino]acetyl]-2(1H)-quinolinone hydrochloride (382mg) and Intermediate 1 (311mg) in ethanol (20ml) was added to a pre-reduced mixture of 10% palladium oxide on carbon (160mg), 5% platinum oxide on carbon (160mg), and anhydrous sodium acetate (158mg) in ethanol (5ml) and hydrogenated. The catalyst and solvent were removed and the residue was treated with aqueous saturated sodium bicarbonate (20ml) and EA (15ml). The precipitate was filtered off, dried in vacuo, and purified by [FCS] eluting with EA-methanol-triethylamine (73:25:2) to give a solid which was adsorbed onto silica gel (Merck 7734, 3g) from methanol. The silica gel plug was applied to [FCS] eluting with EA-methanol-triethylamine (94:5:1+79:20:1) to give, after trituration with ER the title compound as a light yellow solid (63mg), m.p. 134-138°. T.l.c. (Toluene-ethanol-NH₃, 78:20:2) Rf 0.15.

Example 7

4-[1-Hydroxy-2-[[6-(4-phenylbutoxy)hexyl]amino]ethyl]-1,2-benzenediol

A solution of Intermediate 18 (1g) in absolute ethanol (25ml) was hydrogenated over 10% palladium on carbon (0.15g) and 10% platinum on carbon (0.15g) catalysts. The mixture was filtered and evaporated to give a solid which was slurried in ER (25ml) and filtered to give the title catechol as a pale-mauve solid (0.28g) m.p. 126-7° (dec).

T.l.c. triethylamine-deactivated silica (EA-methanol 1:1) Rf 0.72

Example 8

(1R)-4-[1-Hydroxy-2-[[1-methyl-6-(2-phenylethoxy)hexyl]amino]ethyl]-1,2-benzenediol.

Intermediate 1 (1.00g), R-4-(2-amino-1-hydroxyethyl)-1,2-benzenediol (722mg), acetic acid (774mg) and methanol (18ml) were treated with

sodium cyanoborohydride (188mg) at room temperature. The mixture was stirred for 17h, poured into aqueous saturated sodium bicarbonate (25ml), extracted with EA (3x25ml), and the combined, dried (Na_2SO_4) extracts were evaporated. The residue (1.83g) was adsorbed onto silica gel (Merck 7734, 6g) and subjected to [FCS] eluting with EA-methanol-triethylamine (90:9:1) to give a light brown solid (0.26g) which was further purified by chromatography as above to give the title compound as a red solid (67mg), m.p. 116-119°.

Analysis Found:

C, 69.6; H, 8.6; N, 3.65.

$\text{C}_{23}\text{H}_{33}\text{NO}_4 \cdot 0.074\text{Et}_3\text{N} \cdot 0.15\text{H}_2\text{O}$ requires C, 70.8; H, 8.7; N, 3.8%.

Example 9

4-[1-Hydroxy-2-[[5-(4-phenylbutoxy)pentyl]amino]ethyl]-1,2-benzenediol

A solution of Intermediate 20 (1.89g) in absolute ethanol (70ml) was hydrogenated over a mixture of 5% platinum on charcoal (0.2g) and 10% palladium on charcoal (0.2g) catalysts until the uptake of hydrogen ceased. The mixture was filtered through hyflo, evaporated in vacuo and the crude product was purified by [FCS] (triethylamine deactivated silica) eluting with toluene-ethanol (9:1) to give a brown oil.

Trituration with ER gave the title compound as a brown solid (0.21g).

Analysis Found:

C, 68.0; H, 8.2; N, 3.4.

$\text{C}_{23}\text{H}_{33}\text{NO}_4 \cdot \text{H}_2\text{O}$ requires C, 68.1; H, 8.7; N, 3.45%

Example 10

5-[1-Hydroxy-2-[[6-(4-phenylbutoxy)hexyl]amino]ethyl]-1,3-benzenediol

Intermediate 22 (0.53g) in methanol (50ml) was hydrogenated over 10% palladium oxide on carbon (0.26g). The catalyst was removed by filtration through hyflo and the filtrate evaporated at reduced pressure. The resulting green gum was dissolved in EA (10ml) and adsorbed onto silica gel (2g Merck 7734). The dried silica gel plug was applied to [FCS] eluting with triethylamine in EA to give a clear gum. Co-evaporation with ER (2x10ml) gave the title compound as a green friable solid (0.28g) which on standing became a glass, m.p. 37- 39°.

T.l.c. (EA - methanol - triethylamine, 89:10:1) Rf 0.3.

Example 115-[1-Hydroxy-2-[[6-(2-phenylethoxy)hexyl]amino]ethyl]-1,3-benzenediol benzoate (salt)

A solution of Intermediate 25 (0.7g) in ethanol (10ml) and THF (10ml) was hydrogenated over 10% palladium on charcoal (0.1g). The mixture was filtered and evaporated and the residue was purified by [C] eluting with EA-methanol-triethylamine (90:10:1) to give a colourless oil (0.3g). The oil in chloroform (10ml) was treated with benzoic acid (0.15g) in chloroform (5ml) and solvent was evaporated to leave a colourless gum. The gum was triturated with ER (3x15ml) and dried under vacuum to give the title compound as a beige friable solid (0.27g). T.l.c. (EA-methanol-NH₃ 90:10:1) Rf 0.15.

Analysis Found: C, 69.4; H, 7.7; N, 2.8.
 C₂₂H₃₁NO₄·C₇H₆O₂·0.3H₂O requires C, 69.5; H, 7.6; N, 2.8%.

Example 125-[1-Hydroxy-2-[[1-methyl-6-(2-phenylethoxy)hexyl]amino]ethyl]-1,3-benzenediol benzoate (salt)

A solution of 3,5-bis(phenylmethoxy)-α-[[bis(phenylmethyl)amino]-methyl]benzenemethanol (1.0g) and Intermediate 1 (0.44g) in ethanol (30ml) and THF (10ml) was hydrogenated over 10% palladium on charcoal (0.2g) and 5% platinum on charcoal (0.2g). The mixture was filtered and evaporated and the residue was purified by [C] eluting with EA - methanol - triethylamine (90:10:1) to give a colourless oil. A solution of the oil and benzoic acid (0.15g) in chloroform (10ml) was evaporated and the residue was triturated with ER (2x10ml) to give the title compound as an off-white solid (0.42g) m.p. 77-78°. T.l.c. (EA - methanol - NH₃ 9:1:0.1) Rf 0.2

The following compound was prepared in a similar manner to Example 11:

Example 135-[1-Hydroxy-2-[[5-(4-phenylbutoxy)pentyl]amino]ethyl]-1,3-benzenediol benzoate (salt), (0.32g) from Intermediate 26 (1.0g).

T.l.c. (EA-methanol-NH₃ 9:1:0.1) Rf 0.15

Analysis Found: C, 69.6; H, 8.1; N, 2.8.

C₂₃H₃₃NO₄·C₇H₆O₂·0.5H₂O requires C, 69.5; H, 7.8; N, 2.7%.

The following two compounds were prepared in a similar manner to Example 12:-

Example 14

5-[2-[[6-[2-(4-Fluorophenyl)ethoxy]-1-methylhexyl]amino]-1-hydroxyethyl]-1,3-benzenediol, benzoate (salt), (0.6g) from 3,5-bis(phenylmethoxy)- α -[[bis(phenylmethyl)amino]methyl]benzenemethanol (2.2g) and Intermediate 28 (1.0g) m.p. 79-83°. T.l.c. (EA-methanol-NH₃ 90:10:1) Rf 0.25.

Example 15

5-[1-Hydroxy-2-[[6-[2-(4-methoxyphenyl)ethoxy]-1-methylhexyl]amino]ethyl]-1,3-benzenediol, benzoate (salt), (0.75g) from 3,5-bis(phenylmethoxy)- α -[[bis(phenylmethyl)amino]methyl]benzenemethanol (1.9g) and Intermediate 30 (1.0g) m.p. 74-81°. T.l.c. (EA-methanol-NH₃ 90:10:1) Rf 0.2.

Example 16

5-[2-[1,1-Dimethyl-6-(2-phenylethoxy)hexyl]amino]-1-hydroxyethyl]-1,3-benzenediol, benzoate (salt), from Intermediate 33 (1.2g), m.p. 115-119°. T.l.c. (EA-methanol-NH₃ 90:10:1) Rf 0.2, in a similar manner to Example 11.

Example 17

4-[1-Hydroxy-2-[[6-[2-(4-methoxyphenyl)ethoxy]hexyl]amino]ethyl]-1,2-benzenediol

A solution of Intermediate 34 (0.85g) in absolute ethanol (80ml) was hydrogenated over a mixture of pre-reduced 5% platinum on charcoal (200mg) and 10% palladium on charcoal (200mg) catalysts in absolute ethanol (20ml) until the uptake of hydrogen ceased (1.5h). The solution was filtered through hyflo under nitrogen, the solvent evaporated in vacuo, and the residue triturated with ER to give the title compound as a greyish-blue solid (180mg) m.p. 124-125.5° (dec). T.l.c. (Toluene-ethanol-0.88 ammonia solution 39:10:1). Rf 0.24.

0162576

The following are examples of suitable formulations of compounds of the invention. The term "active ingredient" is used herein to represent a compound of the invention.

Tablets

These may be prepared by the normal methods as wet granulation or direct compression.

A. Direct Compression

	<u>mg/tablet</u>
Active ingredient	2.0
Microcrystalline Cellulose USP	196.5
Magnesium Stearate BP	<u>1.5</u>
Compression weight	200.0

The active ingredient is sieved through a suitable sieve and blended with lactose, starch and pregelatinised maize starch. Suitable volumes of purified water are added and the powders are granulated. After drying, the granules are screened and blended with the magnesium stearate. The granules are then compressed into tablets using 7mm diameter punches.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to lactose or the compression weight and using punches to suit.

C. For buccal administration

	<u>mg/tablet</u>
Active ingredient	2.0
Lactose BP	94.8
Sucrose BP	86.7
	<u>mg/tablet</u>
Hydroxypropylmethylcellulose	15.0
Magnesium Stearate BP	<u>1.5</u>
Compression weight	200.0

The active ingredient is sieved through a suitable sieve and blended with the lactose, sucrose and hydroxypropylmethylcellulose. Suitable volumes of purified water are added and the powders are granulated. After drying, the granules are screened and blended with the magnesium stearate. The granules are then compressed into tablets using suitable punches.

The tablets may be film coated with suitable film forming materials, such as hydroxylpropyl methylcellulose, using standard techniques. Alternatively the tablets may be sugar coated.

Capsules

	<u>mg/capsule</u>
Active ingredient	2.0
* Starch 1500	97.0
Magnesium Stearate BP	<u>1.0</u>
Fill weight	100.0

* A form of directly compressible starch.

The active ingredient is sieved and blended with the excipients. The mix is filled into size No. 2 hard gelatin capsules using suitable machinery. Other doses may be prepared by altering the fill weight and if necessary changing the capsule size to suit.

Syrup

This may be either a sucrose or sucrose free presentation.

A. Sucrose Syrup

	<u>mg/5ml dose</u>
Active ingredient	2.0
Sucrose BP	2750.0
Glycerine BP	500.0
Buffer)	

0162576

Flavour)		as required
Colour)		
Preservative)			
Purified Water BP		to	5.0m

The active ingredient, buffer, flavour, colour and preservative are dissolved in some of the water and the glycerine is added. The remainder of the water is heated to dissolve the sucrose and is then cooled. The two solutions are combined, adjusted to volume and mixed. The syrup produced is clarified by filtration.

B. Sucrose-Free

		<u>mg/5ml dose</u>
Active ingredient		2.0mg
Hydroxypropyl methylcellulose USP (viscosity type 4000)		22.5mg
Buffer)	
Flavour)	
Colour)	as required
Preservative)	
Sweetener)	
Purified Water BP	to	5.0ml

The hydroxypropyl methylcellulose is dispersed in hot water, cooled and then mixed with an aqueous solution containing the active ingredient and the other components of the formulation. The resultant solution is adjusted to volume and mixed. The syrup is clarified by filtration.

Metered Dose Pressurised Aerosol

A. Suspension Aerosol

	<u>mg/metered dose</u>	<u>Per can</u>
Active ingredient micronised	0.100	26.40mg
Oleic Acid BP	0.100	2.64mg
Trichlorofluoromethane BP	23.64	5.67g
Dichlorodifluoromethane BP	61.25	14.70

The active ingredient is micronised in a fluid energy mill to a fine particle size range. The Oleic Acid is

mixed with the Trichlorofluoromethane at a temperature of 10-15°C and the micronised drug is mixed into the solution with a high shear mixer. The suspension is metered into aluminium aerosol cans and suitable metering valves, delivering 85mg of suspension are crimped onto the cans and the Dichlorodifluoromethane is pressure filled into the cans through the valves.

B. Solution Aerosol

	<u>mg/metered dose</u>	<u>Per can</u>
Active ingredient	0.055	13.20mg
Ethanol BP	11.100	2.66g
Dichlorotetrafluoroethane BP	25.160	6.04g
Dichlorodifluoromethane BP	37.740	9.06g

Oleic acid BP, or a suitable surfactant e.g. Span 85 (sorbitan trioleate) may also be included.

The active ingredient is dissolved in the ethanol together with the oleic acid or surfactant if used. The alcoholic solution is metered into suitable aerosol containers followed by the trichlorofluoromethane. Suitable metering valves are crimped onto the containers and dichlorodifluoromethane is pressure filled into them through the valves.

Suppositories

Active ingredient	2.0mg
* Witepsol H15 to	1.0g

* A proprietary grade of Adeps Solidus Ph. Eur.

A suspension of the active ingredient in molten Witepsol is prepared and filled, using suitable machinery, into lg size suppository moulds.

Injection for Intravenous Administration

	<u>mg/ml</u>
Active ingredient	0.5mg
Sodium Chloride BP	as required
Water for Injection BP to	1.0ml

Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted, using acid or alkali, to that of optimum stability and/or facilitate solution of the active ingredient. Alternatively suitable buffer salts may be used.

The solution is prepared, clarified and filled into appropriate size ampoules sealed by fusion of the glass. The injection is sterilised by heating in an autoclave using one of the acceptable cycles. Alternatively the solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions. The solution may be packed under an inert atmosphere of nitrogen or other suitable gas.

Inhalation Cartridges

	<u>mg/cartridge</u>
Active ingredient micronised	0.200
Lactose BP to	25.0

The active ingredient is micronised in a fluid energy mill to a fine particle size range prior to blending with normal tableting grade lactose in a high energy mixer. The powder blend is filled into No. 3 hard gelatin capsules on a suitable encapsulating machine. The contents of the cartridges are administered using a powder inhaler such as the Glaxo Rotahaler.

0162576

The stimulant action at β_2 -adrenoreceptors of compounds of the invention was determined using the following:

GUINEA-PIG TRACHEAL STRIP PREPARATION

Tracheal rings were mounted in a superfusion apparatus, and continuously superfused with oxygenated physiological (Kreb's) solution containing indomethacin ($2.4 \times 10^{-6} \text{M}$) and atropine ($4 \times 10^{-7} \text{M}$) at 37° at a rate of 2ml/min. Changes in tension of the preparation were measured using an isometric strain gauge. Preparations were contracted for the duration of the test by the inclusion of prostaglandin $F_{2\alpha}$ ($2.9 \times 10^{-6} \text{M}$) in the superfusion fluid. Two bolus dose-effect curves to the standard, isoprenaline, (1×10^{-12} - 1×10^{-9} moles) were obtained at the start of each test in a cumulative fashion, allowing the relaxation obtained with each to reach its own maximum before the next increment was made. On completion of this dose-effect curve, sufficient time was allowed for the tissue to recover (15-30min). After this time, sequential concentration-effect curves were constructed for first isoprenaline and then the test compound. These were constructed as follows: a low concentration (isoprenaline $3 \times 10^{-10} \text{M}$; test compound $1 \times 10^{-10} \text{M}$) was infused until any response obtained had reached its maximum, then the infusion was stopped and the tissue allowed to recover for a maximum of 30min. After this period the procedure was repeated using progressively increasing concentrations of agonist, and in this way, whole concentration-effect curves obtained. Potency was determined by comparison of the concentration-effect curve thus constructed with that previously obtained for isoprenaline and expressed as equipotent concentration (isoprenaline = 1) i.e. $\frac{EC_{50} \text{ test compound}}{EC_{50} \text{ isoprenaline}}$ was calculated.

Duration of action was also measured for each response, and is the time taken from stopping the infusion to 50% recovery. Graphs were drawn for duration times against response magnitude, and from these, duration times for 50% maximum responses were determined.

0162576

The following potencies (expressed as equipotent concentration, isoprenaline = 1) were determined using the guinea-pig tracheal test described above :-

5

Compound of Example No.		Potency (Isoprenaline = 1)
10	5	0.17
	6	0.16
	8	0.4
15	12	0.15
	14	0.13
	17	0.6

20

In general, the compounds according to the invention are non-toxic at therapeutically useful doses. Thus for example the compounds of Examples 6,7,8 and 10 produced no adverse effects when administered orally to guinea pigs at a dose of 5mg/kg.

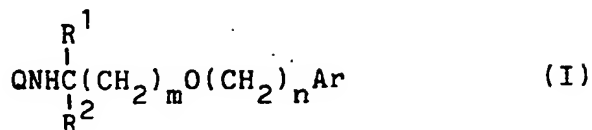
25

30

35

CLAIMS:

1. Compounds of the general formula (I)



wherein

Ar represents a phenyl group optionally substituted by one or two substituents selected from halogen atoms, or C₁₋₃ alkyl or C₁₋₃alkoxy groups, or by an alkylenedioxy group of formula -O(CH₂)_pO- where p is 1 or 2;

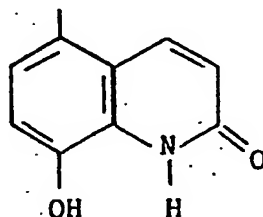
R¹ and R² each represents a hydrogen atom or a C₁₋₃ alkyl group with the proviso that the sum total of carbon atoms in R¹ and R² is not more than 4;

m is an integer from 2 to 8 and

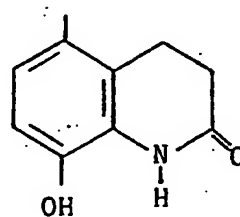
n is an integer from 1 to 7 with the proviso that the sum total of m + n is 4 to 12;

Q represents a group of formula $\text{R}^a\text{CH}(\text{OH})\text{CH}(\text{R}^3)-$ or $\text{R}^b\text{CH}(\text{OH})\text{CH}_2-$,

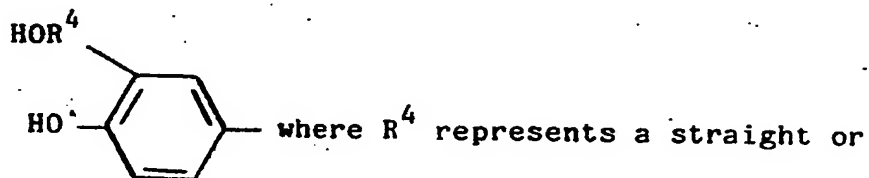
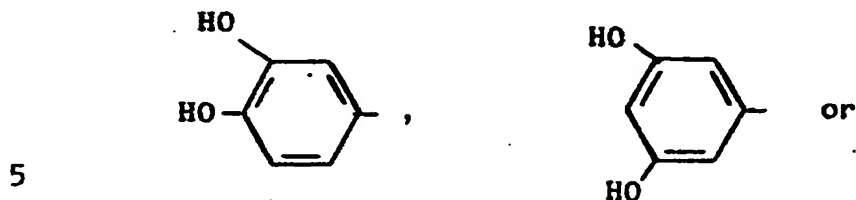
where R³ represents a hydrogen atom or a C₁₋₃ alkyl group, R^a represents :



or



and R^b represents :



10 branched C_{2-3} alkylene chain;
and physiologically acceptable salts and solvates thereof.

2. Compounds as claimed in claim 1 in which the total
number of carbon atoms in the chains $-(CH_2)_m-$ and $-(CH_2)_n-$
is 6 to 12 inclusive.

15

3. Compounds as claimed in claim 1 or 2, in which the
chain $-(CH_2)_m$ is $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$ or
 $-(CH_2)_7-$, and the chain $-(CH_2)_n$ is $-(CH_2)_2-$, $-(CH_2)_3-$,
 $-(CH_2)_4-$, $-(CH_2)_5-$ or $-(CH_2)_6-$.

20

4. Compounds as claimed in any of claims 1 to 3, in
which R^1 and R^2 are each methyl, ethyl, propyl or isopropyl
groups except that if one of R^1 and R^2 is a propyl or
isopropyl group, then the other is a hydrogen atom or a
methyl group.

25

5. Compounds as claimed in any of claims 1 to 4, in which Ar represents a phenyl group substituted by chlorine, bromine, iodine, fluorine, methyl, ethyl, methoxy or ethoxy or Ar represents an unsubstituted phenyl group.

5

6. Compounds as claimed in any of claims 1 to 5, in which in the definition of Q, the group R^3 is a hydrogen atom or a methyl, ethyl, propyl or isopropyl group and the chain R^4 , if present, is $-(CH_2)_2-$, $-(CH_2)_3-$ or $-\underset{\text{CH}_3}{\text{CH}}-$.

10

7. Compounds as claimed in claim 1 which are:-

2-Hydroxy-5-[1-hydroxy-2-[[6-[2-(4-methoxyphenyl)ethoxy]-hexyl]amino]ethyl]benzeneethanol; 2-Hydroxy-5-[1-hydroxy-2-[[1-methyl-6-(2-phenylethoxy)-hexyl]amino]ethyl]benzeneethanol; 5-[1-Hydroxy-2-[[1-methyl-6-(2-phenylethoxy)hexyl]amino]-ethyl-1,3-benzenediol; 5-[1-Hydroxy-2-[[6-(4-phenylbutoxy)hexyl]amino]ethyl]-1,3-benzenediol;

15

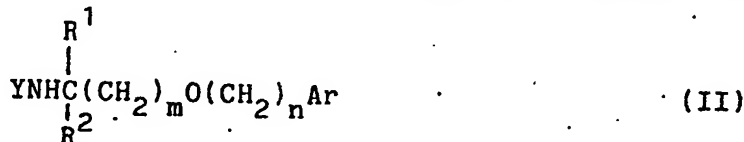
and the physiologically acceptable salts and solvates thereof.

20

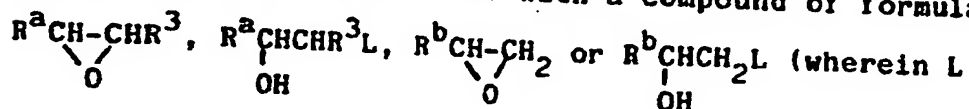
8. A process for the preparation of compounds as claimed in any of claims 1 to 7 or a physiologically acceptable salt or solvate thereof which comprises:

(1) reacting an amine of general formula (II)

25



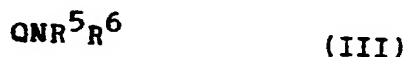
(wherein Y is a hydrogen atom or a group convertible thereto by catalytic hydrogenation) with a compound of formula



5 represents a leaving group) followed, if necessary, by removal of any protecting groups present; or

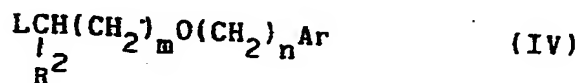
(2a) for the preparation of a compound of formula (I) in which R^1 is a hydrogen atom, alkylating an amine of general formula (III)

10



(wherein R^5 is a hydrogen atom or a protecting group and R^6 is a hydrogen atom) with an alkylating agent of general formula (IV)

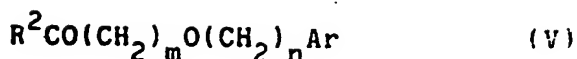
15



(wherein L is a leaving group) followed, if necessary, by removal of any protecting group present; or

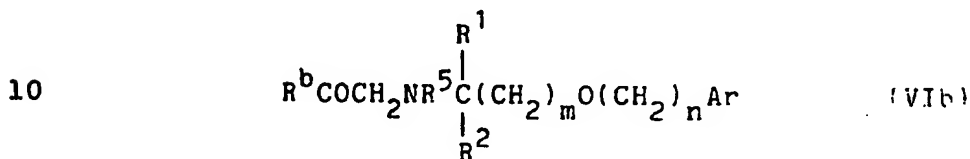
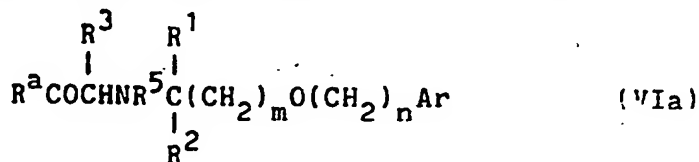
20

(2b) for the preparation of a compound of formula (I) in which R^1 represents a hydrogen atom, alkylating an amine of general formula (III) in which R^5 is a hydrogen atom or a protecting group and R^6 is a hydrogen atom or a group convertible thereto under the reaction conditions, with a
25 compounds of general formula (V)



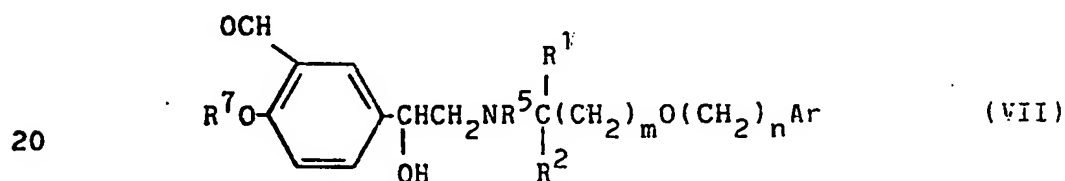
in the presence of a reducing agent followed, if necessary, by removal of any protecting groups present; or

- 5 (3a) reducing a ketone of formula (VIa) or (VIb)



(wherein R^5 is a hydrogen atom or a protecting group followed, if necessary, by removal of any protecting group present; or

- 15 (3b) for the preparation of a compound of general formula (I) in which R^4 is $-CH(CH_3)-$ reacting an aldehyde of general formula (VII)

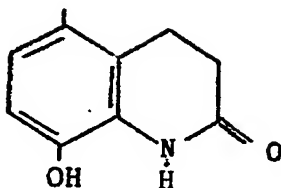


(wherein R^5 and R^7 are each a hydrogen atom or a protecting group) with a Grignard reagent followed, if necessary, by removal of any protecting group present; or

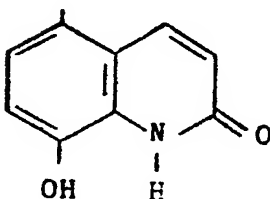
- 25 (4) for the preparation of a compound of formula

0162576

(I) in which R^a is the group



reducing the corresponding compound in which R^a is the group



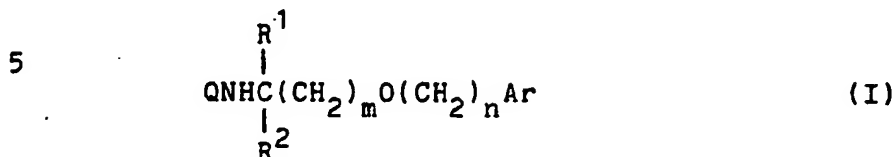
; and

if desired, converting the resulting compound of general formula (I) or a salt thereof into a physiologically acceptable salt or solvate thereof.

9. A pharmaceutical composition comprising at least one compound of general formula (I) as defined in claim 1 or a physiologically acceptable salt or solvate thereof, together with a physiologically acceptable carrier or excipient.

CLAIMS:

1. A process for the production of compounds of the general formula (I)



wherein

Ar represents a phenyl group optionally substituted by one or two substituents selected from halogen atoms, or C₁₋₃ alkyl or C₁₋₃alkoxy groups, or by an alkylenedioxy group of formula -O(CH₂)_p- where p is 1 or 2;

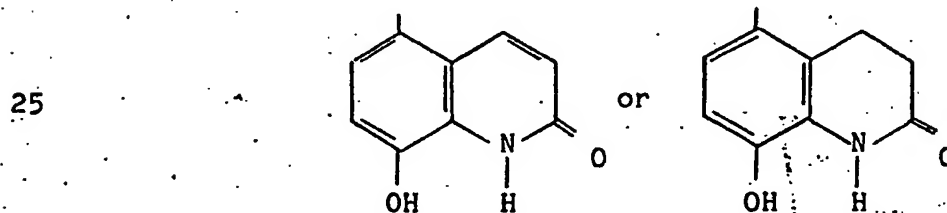
R¹ and R² each represents a hydrogen atom or a C₁₋₃ alkyl group with the proviso that the sum total of carbon atoms in R¹ and R² is not more than 4;

m is an integer from 2 to 8 and

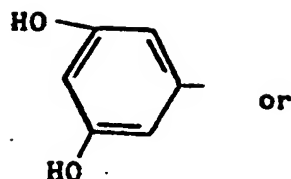
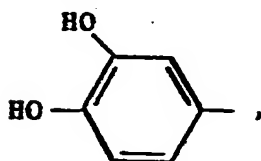
n is an integer from 1 to 7 with the proviso that the sum total of m + n is 4 to 12;

Q represents a group of formula $R^a \begin{array}{c} R^3 \\ | \\ CHCH- \\ | \\ OH \end{array}$ or $R^b \begin{array}{c} CHCH_2- \\ | \\ OH \end{array}$,

where R³ represents a hydrogen atom or a C₁₋₃ alkyl group, R^a represents:

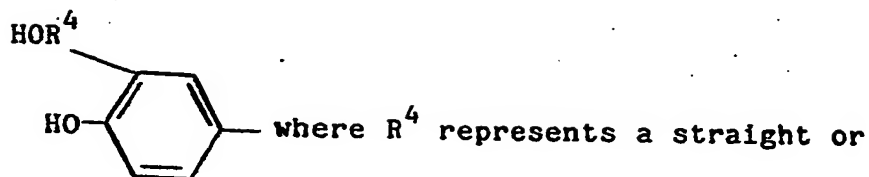


and R^b represents:



or

5

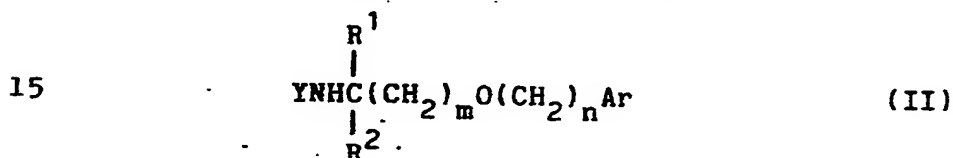


where R^4 represents a straight or

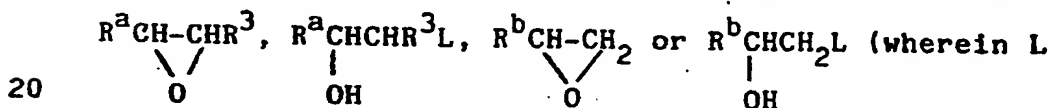
10 branched C_{2-3} alkylene chain;

and physiologically acceptable salts and solvates thereof which comprises:

(1) reacting an amine of general formula (II)



(wherein Y is a hydrogen atom or a group convertible thereto by catalytic hydrogenation) with a compound of formula

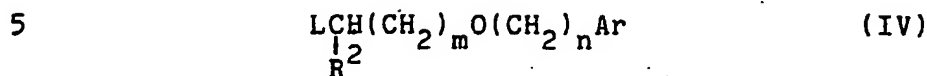


represents a leaving group) followed, if necessary, by removal of any protecting groups present; or

(2a) for the preparation of a compound of formula (I) in which R^1 is a hydrogen atom, alkylating an amine of general formula (III)

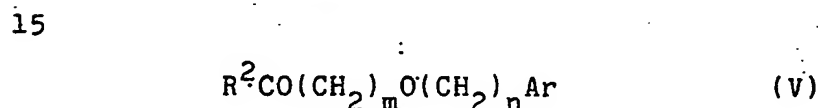


(wherein R^5 is a hydrogen atom or a protecting group and R^6 is a hydrogen atom) with an alkylating agent of general formula (IV)



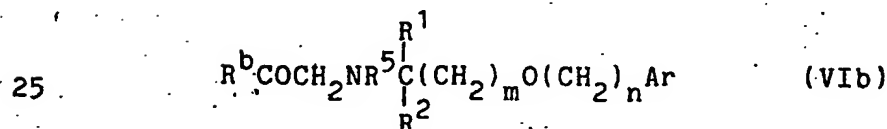
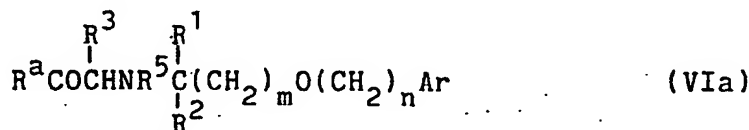
(wherein L is a leaving group) followed, if necessary, by removal of any protecting group present; or

(2b) for the preparation of a compound of formula (I) in which R^1 represents a hydrogen atom, alkylating an amine of general formula (III) in which R^5 is a hydrogen atom or a protecting group and R^6 is a hydrogen atom or a group convertible thereto under the reaction conditions, with a compound of general formula (V)



in the presence of a reducing agent followed, if necessary, by removal of any protecting groups present; or

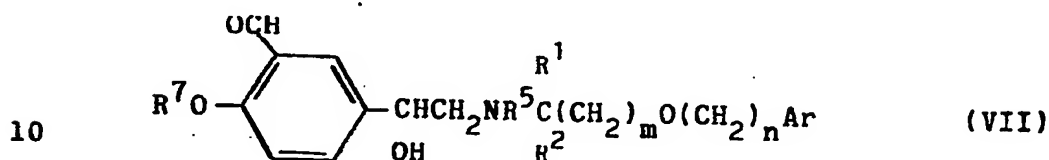
(3a) reducing a ketone of formula (VIa) or (VIb)



0162576

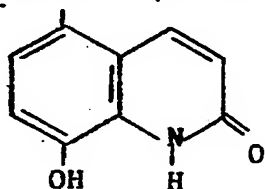
(wherein R^5 is a hydrogen atom or a protecting group) followed, if necessary, by removal of any protecting group present; or

(3b) for the preparation of a compound of general formula (I) in which R^4 is $-\text{CH}(\text{CH}_3)-$ reacting an aldehyde of general formula (VII)

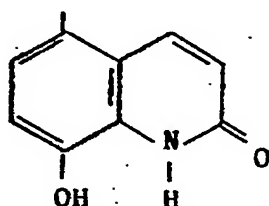


(wherein R^5 and R^7 are each a hydrogen atom or a protecting group) with a Grignard reagent followed, if necessary, by removal of any protecting group present; or

(4) for the preparation of a compound of formula (I) in which R^a is the group



20 reducing the corresponding compound in which R^a is the group



; and

25 if desired, converting the resulting compound of general formula (I) or a salt thereof into a physiologically acceptable salt or solvate thereof.

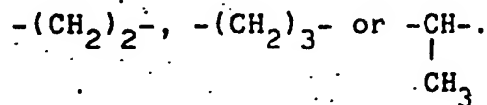
5

10

15

20

25



0162576

7. A process as claimed in claim 1 for the production of compounds which are:-

2-Hydroxy-5-[1-hydroxy-2-[[6-[2-(4-methoxyphenyl)ethoxy]-hexyl]amino]ethyl]benzeneethanol;

5 2-Hydroxy-5-[1-hydroxy-2-[[1-methyl-6-(2-phenylethoxy)-hexyl]amino]ethyl]benzeneethanol;

5-[1-Hydroxy-2-[[1-methyl-6-(2-phenylethoxy)hexyl]amino]-ethyl-1,3-benzenediol;

10 5-[1-Hydroxy-2-[[6-(4-phenylbutoxy)hexyl]amino]ethyl]-1,3-benzenediol;

and the physiologically acceptable salts and solvates thereof.

15

20

25



European Patent
Office

EUROPEAN SEARCH REPORT

0162576
Application number

EP 85 30 2708

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	CHEMICAL ABSTRACTS, vol. 88, no. 1, 2nd January 1978, page 574, no. 6752k, Columbus, Ohio, US; & JP - A - 77 83 379 (OTSUKA PHARMACEUTICAL CO., LTD.) 12-07-1977 * Abstract *	1-9	C 07 D 215/26 C 07 C 93/08 A 61 K 31/135 A 61 K 31/47 // C 07 C 97/00 C 07 C 95/08
A	EP-A-O 021 636 (BEECHAM) * Claims * -----	1-9	
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
			C 07 C 93/00 C 07 D 215/00 A 61 K 31/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 29-08-1985	Examiner PAUWELS G.R.A.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	